Assessing the environment for regulatory change for eicosapentaenoic acid and docosahexaenoic acid nutrition labeling

Amy M Brownawell, William S Harris, Joseph R Hibbeln, David M Klurfeld, Ian Newton, and Allison Yates

This review examines issues related to the development of a recommended daily allowance or adequate intake, two of the categories of dietary reference intakes, for the long-chain omega-3 polyunsaturated fatty acids (omega-3 PUFAs), eicosapentaenoic acid (EPA, 20:5 n-3), and docosahexaenoic acid (DHA, 22:6 n-3). Although some have suggested a dietary intake of two servings of fatty fish per week or supplement intake of 500 mg/day EPA plus DHA, based on evidence from epidemiologic and clinical studies of cardiovascular benefit from regular fish or fish-oil consumption, supplementation with EPA and/or DHA may also have antidepressant and mood-stabilizing effects. Omega-3 PUFA biology is complex and chronic disease outcomes are sometimes difficult to prove, yet the possibility of benefit for a substantial portion of the population from increased omega-3 PUFA intake is a public health issue that must be addressed responsibly and be based on significant scientific evidence.

INTRODUCTION

A conference organized by the Life Sciences Research Office (LSRO) was held on May 1, 2008, to explore issues related to the development of a recommended intake for individuals following the dietary reference intake (DRI) process for the long-chain omega-3 polyunsaturated fatty acids (omega-3 PUFAs), eicosapentaenoic acid (EPA, 20:5 n-3), and docosahexaenoic acid (DHA, 22:6 n-3). Omega-3 PUFAs have a reasonably well-described metabolism, but the effects of intake are complicated by the various sources of omega-3 PUFAs consumed, including fatty fish, flaxseed, and soy-based products, as well as nutritional supplements. Understanding of the complex and significant effects that omega-3 PUFAs have on human biology is evolving rapidly and has expanded beyond cardiovascular effects to include neuropsychological effects such as antidepressant and mood-stabilizing effects.

DIETARY RECOMMENDATIONS IN THE UNITED STATES

Omega-3 polyunsaturated fatty acids

α-linolenic acid (ALA, 18:3 n-3), a plant-based omega-3 PUFA found in foods derived from soybeans, canola, walnuts, olives, flaxseed, and their oils, is not synthesized by humans. Case studies of patients receiving parenteral nutrition with intravenous lipids containing an emulsion of safflower oil, which is very low in ALA but high in omega-6 PUFAs, provide some evidence for the

Affiliations: *AM Brownawell* is with the Life Sciences Research Office, Bethesda, Maryland, USA. *WS Harris* is with the University of South Dakota School of Medicine, Sioux Falls, South Dakota, USA. *JR Hibbeln* is with the National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland, USA. *DM Klurfeld* is with the USDA Agricultural Research Service, Beltsville, Maryland, USA. *I Newton* is with the Ceres Consulting, Markham, Ontario, Canada. *A Yates* is with the USDA Agricultural Research Service, Beltsville, Maryland, USA.

Correspondence: *AM Brownawell*, Life Sciences Research Office, 9650 Rockville Pike, Bethesda, MD 20814-3998, USA. E-mail: brownawella@lsro.org, Phone: +1-301-634-7030, Fax: +1-301-634-7876.

Key words: cardiovascular disease (CVD), dietary reference intake (DRI), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), mood-stabilizing effects

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doi:10.1111/j.1753-4887.2009.00212.x

essentiality of ALA in the diet.[1–4] Neurological and dermatological abnormalities and poor growth were resolved following administration of ALA or soybean oil.[1,2,4] ALA is the 18-carbon chain precursor for the *in vivo* synthesis of its longer-chain derivatives, EPA and DHA, but the efficiency of this conversion is low. Fish, particularly fatty fish, seafood, and certain species of microalgae, are rich sources of EPA and DHA. EPA and DHA may beneficially affect cardiovascular health. EPA and DHA can lower plasma triglyceride levels[5,6] and are documented to have antiarrhythmic and antithrombotic effects.[7] Evidence exists for the role of DHA in neural and visual development and function, especially during pregnancy, lactation, and infancy. Low blood levels of DHA have been associated with impaired visual acuity and brain development in infants.[8] Despite the fact that PUFAs are metabolized for energy rather than tissue repletion when caloric intake is limited, plasma or tissue concentrations of EPA and DHA for the US adult population below which impairment occurs have not been established by national advisory committees. Nationally accepted biomarker-based goals for intakes of EPA and DHA, especially for cardiovascular (e.g., modification of triglyceride levels) and potential neuropsychological endpoints modified by omega-3 PUFAs, are also lacking.

Four categories of dietary reference intakes (DRIs) were established by the Food and Nutrition Board of the Institute of Medicine, part of The National Academy of Sciences: estimated average requirements (EARs), recommended dietary allowances (RDAs), adequate intakes (AIs), and tolerable upper intake levels (ULs).[9] An additional DRI, the acceptable macronutrient distribution range (AMDR), was developed for macronutrients. In its report released in 2002 and published in 2005, the Institute of Medicine's (IOM) Macronutrient Panel concluded that inadequate data (including a lack of dose-response data) were available for setting an EAR and thus did not establish an RDA for omega-3 PUFAs.[10] The EAR is defined as "the daily intake value that is estimated to meet the requirement, as defined by a specific indicator of adequacy, in half the apparently healthy individuals in a subpopulation."[10] The RDA value is set at two standard deviations above the EAR to cover approximately 97% of the population.[11]

While the IOM Macronutrient Panel evaluated the dietary adequacy of ALA, an essential PUFA, the available data were deemed not applicable to the apparently healthy US and Canadian populations, the groups for which DRIs are established. A large proportion of the data available to the panel during the review process involved omega-3 PUFA intake in populations at risk for disease or with established disease (i.e., cardiovascular disease).

An AI, a value typically set when an EAR and RDA cannot be set, was established for ALA (1.6 g/day for men and 1.1 g/day for women) based on the median intake of ALA by adults in the United States where a deficiency is basically non-existent in non-institutionalized populations. The established AMDR for ALA is 0.6–1.2% of energy.[10] The AMDR is the intake range for macronutrients that indicates the consumption levels above and below which the risk of a chronic disease, as well as nutritional inadequacy, is increased.[10] Since EPA and DHA can contribute to omega-3 PUFA intake, and since the median intake of EPA and DHA in the United States is approximately 10% of the total dietary intake, the Macronutrient Panel established that up to 10% of the omega-3 PUFA AI could be satisfied by EPA and DHA.[10,12] No specific recommendation for EPA and/or DHA *per se* was made, however, even though some research supports greater intakes of EPA and DHA as beneficial for the US and Canadian populations, both of which have a high incidence of cardiovascular disease (CVD) and other chronic disorders that may be modified by longer-chain omega-3 PUFA intake.

Cardiovascular disease and omega-3 PUFA intake recommendations

A majority of studies that support increases in omega-3 PUFA intake have investigated the relationship between omega-3 PUFA consumption and primary and secondary prevention of CVD. The American Heart Association (AHA) has released a scientific statement, *Fish Consumption, Fish Oil, Omega-3 Fatty Acids and Cardiovascular Disease*[13] that reviewed the effects of omega-3 PUFAs on a variety of risk factors for coronary heart disease (CHD) including serum lipids, heart function, hemodynamics, and arterial endothelial function. The AHA states that "randomized controlled trials have shown that omega-3 supplements can reduce CVD events (i.e., death, non-fatal heart attacks, and non-fatal strokes). Specifically, EPA and DHA also reduce the risk of arrhythmias, decrease triglyceride levels, slow the growth rate of atherosclerotic plaques, and slightly reduce blood pressure. However, more studies are needed to confirm and further define the health benefits of omega-3 supplements for preventing a first or subsequent CVD event."[13] The AHA recommends that individuals without documented CHD eat a variety of fish (preferably fatty fish) at least twice a week and include oils and foods rich in ALA. Other organizations like the American Diabetes Association and other similar professional organizations also recommend the consumption of two or more servings of fish per week to provide omega-3 PUFAs.[14]

The AHA recommends that patients with documented CHD and individuals with hypertriglyceridemia who need to reduce their serum triglyceride levels consume EPA/DHA supplements under a physician's

care. A prescription medication, LOVAZA® (GlaxoSmith-Kline, Philadelphia, PA, USA; total EPA/DHA = 465/375 mg) has been approved by the FDA to be used along with diet modification to reduce very high levels of blood triglycerides in adults.[15]

Although the 2005 Dietary Guidelines Advisory Committee Report[16] recommended the consumption of two servings of fish/week for the US population, the 2005 *Dietary Guidelines for Americans* (DGA)[17] does not make that recommendation. Instead, the Guidelines state "evidence suggests that consuming approximately 2 servings of fish/week (8 oz total) may reduce the risk of mortality from CHD and that consuming EPA/DHA may reduce the risk of mortality from CVD in people who have already experienced a cardiac event."[17]

FOOD AND DIETARY SUPPLEMENT LABEL REGULATIONS

The nutrition facts label

In 1990, the Nutrition Labeling and Education Act (NLEA) was signed into law amending the Federal Food, Drug, and Cosmetics Act. In response to NLEA, the US Food and Drug Administration (FDA) amended its regulations to establish two sets of label reference values: reference daily intakes (RDIs) and daily reference values (DRVs) for use in declaring the nutrient content of a food on its label. RDIs are reference values from the 1968 RDAs of the Food and Nutrition Board[18]; for most vitamins and minerals they usually represent the highest RDA for adults and children 4 or more years of age, excluding pregnant and lactating women. DRVs are reference intake levels for those nutrients that are important to diet and health (e.g., sodium, potassium, total fat, saturated fat, cholesterol, total carbohydrate, protein, and dietary fiber). The RDI and DRV are used to establish a single label reference value known as the daily value (DV). Two changes have been made to the Nutrition Facts Label since its inception. In 1995, the FDA amended certain RDIs to reflect some of the 1989 NAS RDAs[19] and estimated safe and adequate daily dietary intakes (ESADDIs), instead of being based on RDAs established in 1968, and in 2003 the FDA amended its regulations on nutrition labeling to require *trans* fatty acids be declared in grams per serving.

Although no labeling is required for PUFAs, which includes omega-3 PUFAs, PUFAs can be voluntarily listed on the Nutrition Facts label in grams/serving and factual statements, such as "50 mg omega-3 PUFA", can be provided on the label. The FDA submitted an advance notice of proposed rulemaking (ANPRM) – *Food Labeling: Revision of Reference Values and Mandatory Nutrients* – for public comment about updating the Nutrition/Supplements Facts label. Seventy-five questions were posed, including five questions regarding PUFAs.[20] These questions include the following: 1) Should polyunsaturated fat continue to be voluntary or should it be made mandatory on the food label? 2) Should a daily recommended value (DRV) for polyunsaturated fat (omega-3 plus omega-6) be established using the AMDRs for omega-6 (5–10 %) and omega-3 (0.6–1.2 %) of total calories? If so, should the midpoint be used? 3) Should a DRV for polyunsaturated fat be derived based upon AIs for linoleic acid plus α-linolenic acid? 4) Should separate DRVs for linoleic acid and α-linolenic acid be established? 5) If separate DRVs for linoleic and α-linolenic acid are established should they be made voluntary or mandatory on the food label?

The FDA is currently reviewing the public comments received prior to this ANPRM. A proposed rule will be published in the Federal Register for additional public comment followed by publication of a final rule.

Qualified health claims

The FDA's 2003 *Consumer Health Information for Better Nutrition Initiative* provides for the use of qualified health claims when there is emerging evidence for a relationship between a food or component of a food or dietary supplement and reduced risk of a disease or a health-related condition.[21] The evidence for a qualified health claim does not meet the significant scientific agreement standard required by FDA for issuing an authorized health claim. In 2002 and 2004, FDA issued letters of enforcement discretion for qualified health claims for the labeling of conventional foods and dietary supplements that contain EPA and DHA. The current claim statement is "Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 PUFAs may reduce the risk of CHD. One serving of [name of food] provides [number] grams of EPA and DHA omega-3 PUFAs."[22] The agency did not determine a daily dietary intake level needed to achieve the claimed effect because the scientific evidence for this relationship was viewed as inconclusive and unable to support the establishment of a recommended daily dietary intake level or even a possible level of effect for the general US population.

Nutrient content claims

The NLEA permits the use of label claims that characterize the level of nutrient in a food (i.e., nutrient content claims) made in accordance with the FDA's authorizing regulations.[21] Nutrient content claims describe the level of a nutrient or dietary substance in the product using terms such as "free", "high", and "low", or they compare the level of nutrient in a food to that of another food, using terms

such as "more", "reduced", "lite", "healthy", and "lean". After reviewing the information included in three notifications submitted under the provisions of the Food and Drug Administration Modernization Act of 1997 (FDAMA), the FDA proposed to prohibit nutrient content claims for EPA and DHA because "they are not based on an authoritative statement that identifies a nutrient level to which the claims refer, as required by the controlling statutory authority."[23,24] FDAMA only permits claims based on current, published authoritative statements from "a scientific body of the US with official responsibility for public health protection or research directly related to human nutrition . . . or the National Academy of Sciences or any of its subdivisions."[25] Other scientific bodies specifically identified by FDAMA include the National Institutes of Health and the Centers for Disease Control and Prevention.

USING EVIDENCE-BASED REVIEWS TO EVALUATE NUTRITION

Experts differ on the utility and value of meta-analyses based on systematic reviews to evaluate diet and nutrition. Systematic reviews were initially used to evaluate drugs and devices that often have a large effect in a small population of ill patients (with an untreated control group) that have a monotonic response and sharply defined primary outcome. In contrast, all members of a healthy population consume nutrients; thus, recommendations must be formulated for a large and varied group. Prevention of adverse health effects is the usual goal, intake varies, threshold effects may be observed, multiple systems may be affected, and effects are often small but may, over time, have a large aggregate effect and public health impact. Limitations of such systematic reviews in the field of nutrition include few randomized controlled trials, except for many supplement ingredients, confounding in observational studies, variation in what is consumed (e.g., fish or supplements), lack of dose-response data, and generally lower quality studies. Nevertheless, evidence-based reviews are being used to evaluate diet and nutrition and clearly articulated procedures help establish the expected standard of review.[26]

The FDA has now implemented an evidence-based review system for all health claims and it evaluates the strength of the scientific evidence to support a proposed claim about a substance/disease relationship.[27] "The evaluation process involves a series of steps to assess scientific studies and other data, eliminate those from which no conclusions about the substance/disease relationship can be drawn, rate the remaining studies for methodological quality, and evaluate the strength of the totality of scientific evidence by considering study types, methodological quality, quantity of evidence for and against the claim (taking into account the numbers of various types of studies and study sample sizes), relevance to the US population or target subgroup, replication of study results supporting the proposed claim, and overall consistency of the evidence."[27] The risk of disease can be determined either by incidence of the disease or by measuring surrogate endpoints of disease risk. The surrogate endpoints used for CVD risk are typically total and LDL-cholesterol levels and blood pressure. As discussed below, some benefits of omega-3 PUFAs are not mediated through classic risk factors of CVD, including triglycerides; therefore, the types of studies that could be evaluated for a health claim about omega-3 PUFAs and CVD are potentially limited.

Systematic reviews of omega-3 PUFAs

In 2004 and 2005, the Agency for Healthcare Research and Quality (AHRQ) published evidence reports to summarize the data on the health effects of the omega-3 PUFAs EPA, DHA, ALA, and docosapentaenoic acid (DPA, 22:5 n-3) on CVD,[28,29] cancer,[30] child and maternal health,[31] eye health,[32] asthma,[33] organ transplantation,[34] mental health,[35] neurological diseases,[36] and gastrointestinal, kidney, and autoimmune diseases.[37] The Tufts-New England Medical Center (Tufts-NEMC) Evidence-based Practice Center (EBPC) prepared three reports for AHRQ concerning the health benefits of PUFAs on CVD. In the summary of the report, *Effects of Omega-3 Fatty Acids on Cardiovascular Disease*, Tufts-NEMC concluded that "a number of studies offer evidence to support the hypothesis that fish, fish oil, or ALA supplement consumption reduces all-cause mortality and various CVD outcomes, although the evidence is strongest for fish or fish oil."[29] However, "there is an imbalance in the design of studies available."[29] A majority of primary CVD prevention evidence comes from cohort studies, but most secondary CVD prevention data are derived from randomized controlled trials. Tufts-NEMC EBPC concluded in the summary of its report on the *Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors and Intermediate Markers of Cardiovascular Disease* that measurements of risk factors and intermediate markers of CVD provide additional information about the effects of fish oil on cardiovascular health.[28] The scientists concluded that "there is strong evidence that fish oils have a strong beneficial effect on serum triglyceride levels that is dose-dependent and similar in various populations.[28] In addition "there is also evidence of a very small beneficial effect of fish oils on blood pressure and possible beneficial effects on coronary restenosis after angioplasty, exercise capacity in patients with coronary atherosclerosis, and possibly heart rate variability, particularly in patients with recent myocardial infarctions."[28]

No consistent beneficial effects of omega-3 PUFA consumption on the other outcomes of interest could be drawn by the EBPCs from the published studies. In particular, limitations related to the quality and quantity of evidence was cited repeatedly in the published reports.

Design and data reporting measures suggested by AHRQ to improve omega-3 studies include the following: reporting of the source, type, dose, and method of delivery of omega-3; baseline assessments of omega-3 and omega-6 intake, including an estimated omega-6 : omega-3 intake ratio; inclusion of a control group not receiving omega-3; US population-based studies, because dietary differences limit applicability of data based on other populations; and dietary reporting of participants' background diet and fish consumption, particularly the type of fish consumed and the method of preparation. Many of these measures could be easily included in future studies and would substantially bolster the quality of published studies and allow better comparisons between different studies and populations.

OMEGA-3 PUFAS AND OTHER HEALTH EFFECTS

Suggested dietary intakes of two servings of fish, preferably fatty fish, per week, or 500 mg/day EPA and DHA are based on evidence from epidemiologic and clinical studies demonstrating cardiovascular health benefits from regular fish or fish-oil consumption.[12,14,38] It appears that some benefits of omega-3 PUFAs are not mediated through classic or emerging CHD risk factors, but may instead be mediated through membrane effects (e.g., platelet aggregation, heart rate, and heart rate variability). For example, the omega-3 index, a measurement of the amount of EPA and DHA in red blood cell membranes expressed as the percent of total PUFAs, may help to define risk and ultimately help define a US target intake for EPA and DHA for healthy adults if it becomes accepted as a measure of adequacy that is related to a specific health outcome.[39,40]

Although much emphasis has been placed on the potential cardiovascular benefits of consuming EPA and DHA, a few studies have shown that supplementation with EPA and/or DHA can have antidepressant and mood-stabilizing effects that may aid in the treatment of psychiatric disorders such as major depression, postpartum depression, and bipolar disorder.[41,42] Countries with greater *per capita* rates of seafood consumption have lower reported rates of major depression, post-partum depression, and mortality from homicide.[43,44] There is also increasing interest in the role of omega-3 PUFAs in the treatment and prevention of behavioral disorders, such as attention deficit hyperactivity disorder and the onset of age-related neurodegenerative disease.[41] The evidence for effects on aggression, depression, and cognitive function is largely epidemiological, but consistent with tissue compositional studies and meta-analyses of randomized clinical trials in depression.[45] However, uncertainty remains as to the mechanisms of action of omega-3 PUFAs in psychiatric disorders.

CONCLUSION

Discussion during the LSRO conference pointed out that the path towards regulatory change for product labeling and health claims for omega-3 PUFAs begins with the setting of a DRI by the IOM for EPA and DHA based on decreasing risk of chronic disease. New research has been published since omega-3 PUFAs were reviewed by the Macronutrient Panel, and this information deserves evaluation. Additional, better-designed observational and clinical studies must be conducted and additional health outcomes upon which to base regulatory decisions need to be defined. Also, evaluations should include data on molecular connections in the competitive metabolic interactions of omega-3 and omega-6 fats to clarify if, and how, diet imbalances cause disease consequences. At the LSRO conference it was noted that the details required to perform meta-analyses of nutrition studies, such as dose-response data, identification of many potential confounding effects, and accurate dietary recall data, are often unavailable. Critical data regarding individual responses should be published in journal articles or be made available online as supplemental material at either the journal's or the investigator's Web site. Experimental methods and data analysis should be equally transparent. New paradigms with which to interpret the current data should be considered and, following identification of the limitations of the current data, research to fill in information gaps should be supported to stimulate new government-funded research. Omega-3 biology is complex, and chronic disease outcomes are sometimes difficult to prove, yet the possibility that a substantial portion of the population might benefit from increased omega-3 intake is important enough a public health issue of significant enough import that it must be addressed in an expedient and responsible manner.

Acknowledgments

Funding. The Life Sciences Research Office Workshop held on May, 1 2008, in Bethesda, Maryland, and this manuscript have been supported by funding from the Global Organization for EPA and DHA Omega-3 (GOED). Workshop details and speaker presentations can be found at http://www.LSRO.org.

Declaration of interest. WSH is a scientific consultant to the following companies with interests in omega-3 fatty

acids: Monsanto, GlaxoSmithKline (GSK), and Omega-Quant Analytics. *WSH* has received research grants from both Monsanto and GSK, and is on GSK's speakers' bureau. *IN* has consulted for commercial organizations/companies that have or may derive revenues from EPA/DHA products in the future. The remaining authors have no conflicts to report.

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